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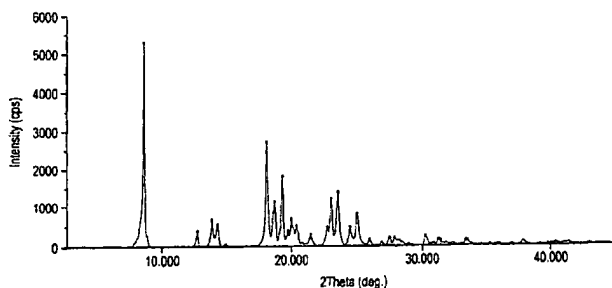
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[Continued on next page]

(54) Title: PROCESS FOR PREPARATION OF HYDRATES OF OLANZAPINE AND THEIR CONVERSION INTO CRYSTALLINE FORMS OF OLANZAPINE



Peak No.	2Theta	FWHM	d-value	Intensity	I/I <sub>0</sub>
1	8.820	0.118	10.0176	5301	100
2	12.820	0.141	6.8995	385	7
3	13.920	0.188	6.3567	654	12
4	14.340	0.212	6.1714	558	11
5	18.180	0.165	4.8756	2721	51
6	18.760	0.235	4.7262	1141	22
7	19.320	0.165	4.5904	1799	34
8	19.740	0.118	4.4937	388	7
9	20.020	0.165	4.4315	663	13
10	20.440	0.188	4.3414	520	10
11	21.440	0.188	4.1411	300	6
12	22.680	0.141	3.9174	478	9
13	22.980	0.188	3.8669	1208	23
14	23.480	0.212	3.7857	1359	26
15	24.380	0.141	3.6480	489	9
16	24.920	0.212	3.5701	799	15
17	25.840	0.212	3.4451	180	3
18	27.420	0.188	3.2500	205	4
19	27.800	0.165	3.2065	200	4
20	30.120	0.141	2.9646	258	5
21	31.120	0.141	2.8715	162	3
22	31.280	0.118	2.8572	147	3
23	33.320	0.141	2.6868	134	3
24	33.480	0.118	2.6743	135	3

(57) Abstract: The present invention relates to a method for the preparation of hydrates of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b] [1,5] benzodiazepine (hereinafter referred to as Olanzapine). The present invention also relates to a process for conversion of these hydrates into a pure crystalline form of olanzapine referred to as form-I. The present invention also relates to a method of converting Olanzapine Form-2 to Form-1.

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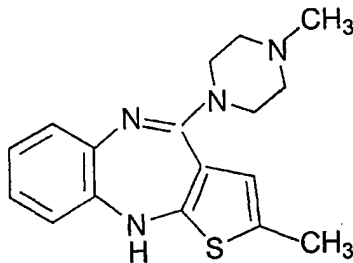
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## PROCESS FOR PREPARATION OF HYDRATES OF OLANZAPINE AND THEIR CONVERSION INTO CRYSTALLINE FORMS OF OLANZAPINE

The present invention relates to a method for the preparation of hydrates of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b] [1,5] benzodiazepine (hereinafter referred to as Olanzapine). The present invention also relates to a process for conversion of these hydrates into a pure crystalline form of olanzapine referred to as form-I. The present invention also relates to a method of converting Olanzapine Form-2 to Form-1.

This invention more particularly relates to the preparation of hydrates of olanzapine and their conversion into crystalline form of Olanzapine Form-1 through recrystallization from a solvent. Olanzapine is represented by the following structure.



Olanzapine

Olanzapine is useful for treating psychotic patients and mild anxiety states. Preparation of Olanzapine and its acid salts, having pharmaceutical properties particularly in the treatment of disorders of the central nervous system has been discussed in U.S. Patent No. 5,229,382.

U.S. Patent No. 5,229,382 does not refer to any specific polymorphic crystalline form of Olanzapine. European patent specification No. 733635A1 claims Form-2 of Olanzapine. The process under this patent describes preparation of Form-2 from ethyl acetate. This patent also designated the product obtained according to the process described in U.S. Patent No. 5,229,382 as Form-1.

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Furthermore, EP 733635A1 discloses the d values for Form-1 and Form-2 from their X-ray Diffractograms. The values are:

	<b>d value</b>	<b>d value</b>
	<b>Form-1</b>	<b>Form-2</b>
5	9.94	10.26
	8.55	8.57
	8.24	7.47
	6.88	7.12
	6.37	6.14
10	6.24	6.07
	5.58	5.48
	5.30	5.21
	4.98	5.12
	4.83	4.98
15	4.72	4.76
	4.62	4.71
	4.53	4.47
	4.46	4.33
	4.29	4.22
20	4.23	4.14
	4.08	3.98
	3.82	3.72
	3.74	3.56
	3.69	3.53
25	3.58	3.38
	3.50	3.25
	3.33	3.12

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	3.28	3.08
	3.21	3.06
	3.11	3.01
	3.05	2.87
5	2.94	2.81
	2.81	2.72
	2.75	2.64
	2.65	2.60
	2.63	
10	2.59	

It is noteworthy to mention that **EP 0 831 098 A2** discloses the preparation of a series of dihydrates of olanzapine namely Dihydrate B, Dihydrate D and Dihydrate E. The d values from the X-ray Diffractograms for these forms are listed in **EP 0 831 098 A2**.

15 We conducted experiments to obtain Olanzapine Form I by recrystallization of olanzapine from acetonitrile using the process described in Example 1, sub example 4 of U.S. Patent No. 5,229,382. The process is described herein for reference: A mixture of 4-amino-2-methyl-10H-thieno-[ 2,3-b] [1,5]benzodiazepine HCl (100 g), N-methyl piperizine (350ml), DMSO (465 ml) and toluene (465 ml) was heated to  
20 reflux. The reaction mass was maintained at reflux for 19 hours and then cooled to 50°C and water was added. The reaction mass was cooled to 0–10°C and stirred at the same temperature for 6 hours. The crude Olanzapine separated was filtered and dried in oven to a constant weight (76.5 g). The crude compound was added to acetonitrile (750 ml) at boiling temperature. The mixture was boiled for further 5  
25 minutes. The mixture was filtered to remove the undissolved solid. The filtrate was treated with carbon and filtered. The filtrate was distilled to a minimum volume,

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cooled to 0-5°C and maintained at the same temperature for 1.0 hour and filtered.  
The compound was dried to a constant weight in an oven (51.6g).

The polymorphic form obtained from these experiments was characterized for its X-ray Powder Diffraction on Rigaku D / Max 2200. As clearly observed, the d values for this product (Fig. 1) matched with those of Olanzapine Form-2 claimed in EP 733635A1. It is therefore inferred that the recrystallization of Olanzapine in acetonitrile produces Form-2 and not Form-1.

Accordingly, the present invention provides a novel method for preparation of hydrates of olanzapine, which are different from those reported in the literature.

10 These hydrates are named Olanzapine monohydrate-I and Olanzapine dihydrate-I for convenience.

Accordingly, the present invention also provides a novel method for preparation of Olanzapine Form-1 by recrystallization of olanzapine or its hydrates in dichloromethane.

15 The present invention also provides a novel method for converting Olanzapine Form-2 to Olanzapine Form-1

According to the present invention the process for the preparation of olanzapine monohydrate-I comprises:

- a) refluxing a mixture of 4-amino-2-methyl-10H-thieno-[2,3-b] [1,5]benzodiazepine hydrochloride, N-methyl piperazine, dimethyl sulfoxide (DMSO) and toluene for 5 to 20 hours;
- b) cooling the mixture to 20 to 90°C;
- c) adding water;
- d) cooling the mixture to -5 to 25°C and stirring for 2-10 hours;
- 25 e) filtering the mixture and washing with water; and
- f) drying at 30 to 50°C to a constant weight.

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According to the present invention the process for the preparation of olanzapine dihydrate -I comprises:

- a) refluxing a mixture of 4-amino-2-methyl-10H-thieno-[2,3-b] [1,5]benzodiazepine hydrochloride, N-methyl piperazine, dimethyl sulfoxide (DMSO) and toluene for 5 to 20 hours;
- b) cooling the mixture to 20 to 90°C;
- c) adding water;
- d) cooling the mixture to -5 to 25°C and stirring for 2-10 hours;
- e) filtering the mixture and washing with water; and
- f) drying at ambient temperature to a constant weight.

The preferred ratio of 4-amino-2-methyl-10H-thieno-[ 2,3-b] [1,5] benzodiazepine HCl, N-methyl piperazine, DMSO and toluene that can be used for preparation of the monohydrate and dihydrate are:

N-methyl piperazine (2.0 - 8.4 moles with respect to 1.0 mole of 4-Amino-2-methyl-10H-thieno-[ 2,3-b] [1,5]benzodiazepine HCl).

DMSO (2 - 8 times by volume with respect to 1.0 mole of 4-Amino-2-methyl-10H-thieno-[ 2,3-b] [1,5]benzodiazepine HCl).

Toluene (3 - 8 times by volume with respect to 1.0 mole of 4-Amino-2-methyl-10H-thieno-[ 2,3-b] [1,5]benzodiazepine HCl).

According to this invention, Olanzapine Form -I is prepared by heating to reflux a suspension of olanzapine or its hydrates in dichloromethane wherein the amount of dichloro-methane used is 4.5 to 13 volume/weight of Olanzapine to obtain a clear solution. The resultant solution is then treated with carbon followed by filtration. Upon completion of this step the filtrate is cooled to 0 to 5°C and stirred at the same temperature for 60-90 minutes. The separated solid was filtered and washed with dichloromethane. The product obtained on drying in an oven at 60-70°C to a constant weight is Form-1 of Olanzapine.

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The process described in U.S. 5,229,382 was used to prepare olanzapine crude and the process described in EP 733 635 A1 was used to prepare olanzapine Form-2 for our studies. However, other methods may be used to prepare olanzapine crude and olanzapine Form-2 and any other methods that can be used to prepare olanzapine crude and olanzapine Form 2 can be used in the processes of this invention.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the invention.

### **PREPARATION OF OLANZAPINE MONOHYDRATE-1**

#### **EXAMPLE 1**

10 A mixture of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine hydrochloride (20 Kg), N-methyl piperazine (42 lit), dimethyl sulfoxide (40 lit) and toluene (95 lit) was heated to reflux. The reaction mass was maintained at reflux for 17 hours and 15 minutes and then cooled to 40–50°C. Water (95 lit) was added slowly at 40–50°C. The reaction mass was cooled to –0.6 to 1.2°C and stirred at the same temperature for six hours. The Olanzapine crude that separated was filtered and washed with water (10 lit). The product was dried at 30.5 to 31.8°C for 10 hrs and 50 minutes. Yield: 20 Kg. A 20 gm sample from the above material after prolonged heating for an additional 72 hours gave the product with a moisture content of 5.22%.

### **PREPARATION OF OLANZAPINE DIHYDRATE-I**

#### **EXAMPLE 2**

20 A mixture of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine hydrochloride (200 g), N-methyl piperazine (420 ml), dimethyl sulfoxide (200 ml) and toluene (940 ml) was heated to reflux. The reaction mass was maintained at reflux for 12 hours and then cooled to 40°C. Water (940 ml) was added slowly at 40–44°C. 25 The reaction mass was cooled to 0–5°C and stirred at the same temperature for five hours. The Olanzapine crude that separated was filtered and washed with water (100



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ml). The solid obtained was dried atmospherically (25–35°C) for 24 hours (Yield : 241 g).

### **PREPARATION OF FORM-1**

#### **EXAMPLE 3**

- 5        Crude 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5] benzodiazepine (35.0 g) was suspended in dichloromethane (160.0 ml). The suspension was heated to reflux to obtain a clear solution. The resultant solution was then treated with carbon (3.5 g) followed by filtration. Upon completion of this step the filtrate was cooled to 0 to 5°C and stirred at the same temperature for one hour.
- 10    The separated solid was filtered and washed with chilled dichloromethane (10.0ml). The product obtained on drying in oven at 65 to 70°C to a constant weight gave Form-1 of Olanzapine (Yield 22.0 g).

### **CONVERSION OF FORM-2 TO FORM-1**

#### **EXAMPLE 4**

- 15        The stirred suspension of pure form-2 of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine (20.0 g) in dichloromethane (90.0 ml) was heated to reflux to obtain a clear solution. The clear solution was filtered and the filtrate was then cooled to 3 to 5°C and stirred at same temperature for one hour. The crystalline solid separated was filtered and washed with dichloromethane (4.0 ml).
- 20    Subsequent drying at 60 to 70°C to a constant weight yielded Olanzapine Form-1. (Yield: 12.7 g).

### **PREPARATION OF FORM-1 FROM MONOHYDRATE-I OF OLANZAPINE**

#### **EXAMPLE 5**

- 25        Monohydrate-I of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5] benzo- diazepine (25.0 g) prepared as per Example-1 was suspended in dichloromethane (325.0 ml). The suspension was heated to reflux to obtain a clear solution. The resultant solution was then treated with carbon (2.5 g) followed by

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filtration. Upon completion of this step the filtrate was distilled to a minimum volume and then cooled to 2 to 4°C and stirred at the same temperature for 90 minutes. The product separated was filtered and washed with chilled dichloromethane (10 ml). The product obtained on drying in oven at 60 to 70°C to a constant weight gave Form-1 of Olanzapine (Yield 16.5 g)

### **PREPARATION OF FORM-1 FROM DIHYDRATE-I OF OLANZAPINE**

#### **EXAMPLE 6**

Dihydrate-I of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5] benzodiazepine (40.0 g) prepared as per Example-2 was suspended in dichloromethane (520.0 ml). The suspension was heated to reflux to obtain a clear solution. The resultant solution was then treated with carbon (4.0 g) followed by filtration. Upon completion of this step the filtrate was distilled to a minimum volume and the left over reaction mass was cooled to 0 to 2°C and stirred at the same temperature for one hour. The separated solid was filtered and washed with dichloromethane (10.0ml). The product obtained on drying in oven at 65 to 70°C to a constant weight renders Form-1 of Olanzapine (Yield 26.0 g).

The aforementioned crystalline forms in examples 1 to 6 have been examined for their structural and analytical data viz., Powder X-Ray Diffraction, Differential Scanning Calorimetry, and Infrared Absorption Spectroscopy. The results obtained are discussed and the respective drawings attached (Fig. 2 -19).

The X-Ray Diffraction Pattern set out herein for examples 1 to 6 were obtained using Rigaku D / Max-2200 X-Ray Powder Diffractometer having a copper K radiation source of wavelength  $\lambda=1.54 \text{ \AA}$ . The samples were scanned between 3-45 degrees  $2\theta$ .

The d values for the monohydrate-1 in Example-1 are herewith enclosed (Fig. 2).

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	d value	I/I <sub>0</sub>
	10.0176	100
	6.8995	7
	6.3567	12
5	6.1714	11
	4.8756	51
	4.7262	22
	4.5904	34
	4.4937	7
10	4.4315	13
	4.3414	10
	4.1411	6
	3.9174	9
	3.8669	23
15	3.7857	26
	3.6480	9
	3.5701	15
	3.4451	3
	3.2500	4
20	3.2065	4
	2.9646	5
	2.8715	3
	2.8572	2

The d values for the dihydrate-1 in Example-2 are herewith given (Fig. 5).

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	d value	I/I <sub>0</sub>
	9.9949	100
	9.6887	7
	7.0418	2
5	6.4117	2
	6.2495	7
	6.1205	6
	5.4534	6
	5.2358	2
10	4.8230	33
	4.7162	9
	4.5717	15
	4.4847	6
	4.3924	8
15	4.3080	4
	4.2070	3
	4.0735	3
	3.9974	3
	3.9242	9
20	3.8438	12
	3.7699	9
	3.7386	13
	3.6837	3
	3.6509	4
25	3.6072	5
	3.5256	11
	3.4242	2

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	3.1773	2
	3.1207	2
	2.9917	2
	2.9569	3
5	2.8733	2
	2.8483	2

The X-Ray Diffraction Pattern obtained for the products from examples 3 to 6 is identical with those reported in **EP 733 635 A1**.

### **BRIEF DESCRIPTION OF DRAWINGS**

10 Fig. 1 is a characteristic X-ray powder diffraction pattern of Form-2 obtained on recrystallization with acetonitrile (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees)).

Fig. 2 is a characteristic X-ray powder diffraction pattern of Olanzapine monohydrate-I (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta  
15 (degrees)).

Fig. 3 is a characteristic infrared absorption spectrum in potassium bromide of Olanzapine monohydrate-I (Vertical axis, Transmission (%); Horizontal axis: Wave number ( $\text{cm}^{-1}$ )).

Fig. 4 is a characteristic of differential scanning calorimetry thermogram of  
20 Olanzapine monohydrate-I. (Vertical axis: mW; Horizontal axis: Temperature ( $^{\circ}\text{C}$ )).

Fig. 5 is a characteristic X-ray powder diffraction pattern of Olanzapine dihydrate-I (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees)).

Fig. 6 is a characteristic infrared absorption spectrum in potassium bromide of Olanzapine dihydrate-I. (Vertical axis, Transmission (%); Horizontal axis: Wave  
25 number ( $\text{cm}^{-1}$ )).

Fig. 7 is a characteristic of differential scanning calorimetry thermogram of Olanzapine dihydrate-I. (Vertical axis: mW; Horizontal axis: Temperature ( $^{\circ}\text{C}$ )).

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Fig. 8 is a characteristic X-ray powder diffraction pattern of Form-1 produced by recrystallizing crude Olanzapine in dichloromethane. (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees)).

Fig.9 is a characteristic infrared absorption spectrum in potassium bromide of Form-1 produced by recrystallizing crude Olanzapine in dichloromethane. (Vertical axis, Transmission (%); Horizontal axis: Wave number ( $\text{cm}^{-1}$ )).

Fig.10 is a characteristic of differential scanning calorimetry thermogram of Form-1 produced by recrystallizing crude Olanzapine in dichloromethane. [Vertical axis: mW; Horizontal axis: Temperature ( $^{\circ}\text{C}$ )].

Fig.11 is a characteristic X-ray powder diffraction pattern of Form-I obtained on conversion of Form-2 to Form-1 Olanzapine in dichloromethane (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees)).

Fig.12 is a characteristic infrared absorption spectrum in potassium bromide of Form-1 obtained on conversion of Form-2 to Form-1 Olanzapine in dichloromethane (Vertical axis, Transmission (%); Horizontal axis: Wave number ( $\text{cm}^{-1}$ )).

Fig.13 is a characteristic of differential scanning calorimetry thermogram of Form-1 obtained on conversion of Form-2 to Form-1 Olanzapine in dichloromethane (Vertical axis: mW; Horizontal axis: Temperature ( $^{\circ}\text{C}$ )).

Fig.14 is a characteristic X-ray powder diffraction pattern of Form-1 obtained on conversion of olanzapine monohydrate-I to Form-1 Olanzapine in dichloromethane (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees)).

Fig.15 is a characteristic infrared absorption spectrum in potassium bromide of Form-1 obtained on conversion of olanzapine monohydrate-I to Form-1 Olanzapine in dichloromethane (Vertical axis, Transmission (%); Horizontal axis: Wave number ( $\text{cm}^{-1}$ )).

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Fig.16 is a characteristic of differential scanning calorimetry thermogram of Form-1 obtained on conversion of olanzapine monohydrate-I to Form-1 Olanzapine in dichloromethane. (Vertical axis: mW; Horizontal axis: Temperature ( $^{\circ}\text{C}$ )).

5 Fig.17 is a characteristic X-ray powder diffraction pattern of Form-1 obtained on conversion of olanzapine dihydrate-I to Form-1 Olanzapine in dichloromethane (Vertical axis: Intensity (CPS); Horizontal axis: Two Theta (degrees)).

10 Fig.18 is a characteristic infrared absorption spectrum in potassium bromide of Form-1 obtained on conversion of olanzapine dihydrate-I to Form-1 Olanzapine in dichloromethane. ([Vertical axis, Transmission (%); Horizontal axis: Wave number ( $\text{cm}^{-1}$ )]).

Fig.19 is a characteristic of differential scanning calorimetry thermogram of Form-1 obtained on conversion of olanzapine dihydrate-I to Form-1 Olanzapine in dichloromethane. (Vertical axis: mW; Horizontal axis: Temperature ( $^{\circ}\text{C}$ )).

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CLAIM

1. A compound which is Olanzapine monohydrate-I.
2. A compound which is Olanzapine dihydrate-I.
3. A compound which is Olanzapine monohydrate-I having a X-ray powder  
5 diffraction pattern as represented by the following:

	d value	I/I <sub>0</sub>
	10.176	100
	6.8995	7
	6.3567	12
10	6.1714	11
	4.8756	51
	4.7262	22
	4.5905	34
	4.4937	7
15	4.4315	13
	4.3414	10
	4.1411	6
	3.9174	9
	3.8669	23
20	3.7857	26
	3.6480	9
	3.5701	15
	3.4451	3
	3.2500	4
25	3.2065	4
	2.9646	5
	2.8715	3



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2.8572 3

2.6868 3

2.6743 3

4. A compound which is Olanzapine dihydrate-I having a X-ray powder  
5 diffraction pattern as represented by the following:

	D value	I/I <sub>0</sub>
	9.9949	100
	9.6887	7
	7.0418	2
10	6.4117	2
	6.2495	7
	6.1205	6
	5.4534	6
	5.2358	2
15	4.8230	33
	4.7162	9
	4.5717	15
	4.4847	6
	4.3924	8
20	4.3080	4
	4.2070	3
	4.0735	3
	3.9974	3
	3.9242	9
25	3.8438	12
	3.7699	9
	3.7386	13

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	3.6837	3
	3.6509	4
	3.6072	5
	3.5256	11
5	3.4242	2
	3.1773	2
	3.1207	2
	2.9917	2
	2.9569	3
10	2.8733	2
	2.8483	2
	2.7895	2

5. A process for preparing olanzapine monohydrate-I which comprises the steps of:

15 a) refluxing a mixture of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine hydrochloride, N-methyl piperazine, dimethyl sulfoxide and toluene for 5 to 20 hours;

b) cooling the mixture to 20 to 90°C;

c) adding water;

20 d) cooling the mixture to -5 to 25°C and stirring for 2-10 hours;

e) filtering the mixture and washing with water; and

f) drying at 30 to 50°C to a constant weight.

6. The process according to claim 5, wherein the amounts of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine hydrochloride and N-methyl piperazine  
25 are in the ratio of 1:2.0-8.4.

7. The process according to claim 5, wherein the volume of dimethyl sulfoxide

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is 2-8 times the number of moles of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine hydrochloride.

8. The process according to claim 5, wherein the volume of toluene is 3-8 times the number of moles of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]

5 benzodiazepine hydrochloride and dimethyl sulfoxide.

9. A process for preparing olanzapine dihydrate -I which comprises the steps of:

a) refluxing a mixture of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]

benzodiazepine hydrochloride, N-methyl piperazine, dimethyl sulfoxide and toluene for 5 to 20 hours;

10 b) cooling the mixture to 20 to 90°C;

c) adding water;

d) cooling the mixture to -5 to 25°C and stirring for 2-10 hours;

e) filtering the mixture and washing with water; and

drying at ambient temperature to a constant weight.

15 10. The process according to claim 9, wherein the amounts of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]-benzodiazepine hydrochloride and N-methyl piperazine are in the ratio of 1:2.0-8.4.

11. The process according to claim 9, wherein the volume of dimethyl sulfoxide is 2-8 times the number of moles of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5]

20 benzodiazepine hydrochloride.

12. The process according to claim 9, wherein the volume of toluene is 3-8 times the number of moles of 4-amino-2-methyl-10H-thieno-[2,3-b][1,5] benzodiazepine hydrochloride.

13. A process for preparing Olanzapine Form-1 from Olanzapine dihydrate-I  
25 which comprises the steps of:

a) stirring 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]

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benzodiazepine (olanzapine monohydrate -I) in dichloromethane at reflux to obtain a clear solution;

- b) treating the solution with carbon;
- c) filtering the solution to obtain a filtrate;
- 5 d) cooling the filtrate to 0 to 5 ° C
- e) stirring for 60-90 minutes;
- f) filtering to obtain a solid, washing and drying at 60° to 70°C

to a constant weight.

14. The process according to claim 13, wherein in step f) the solid is washed with  
10 dichloromethane.

15. The process according to claim 13, wherein the amount of dichloromethane used in step a) is 4.5 to 13 volume/weight of 2-methyl-10H-thieno[2,3-b][1,5] benzodiazepine hydrochloride.

16. A process for preparing olanzapine Form-1 from olanzapine monohydrate-I  
15 which comprises the steps of:

- a) stirring 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine in dichloromethane at reflux to obtain a clear solution;
- b) treating the solution with carbon;
- c) filtering the solution to obtain a filtrate;
- 20 d) cooling the filtrate to below 0 to 5°C; and
- e) stirring for 60-90 minutes,
- f) separating the solid, washing and drying at 60° to 70°C. to a constant weight.

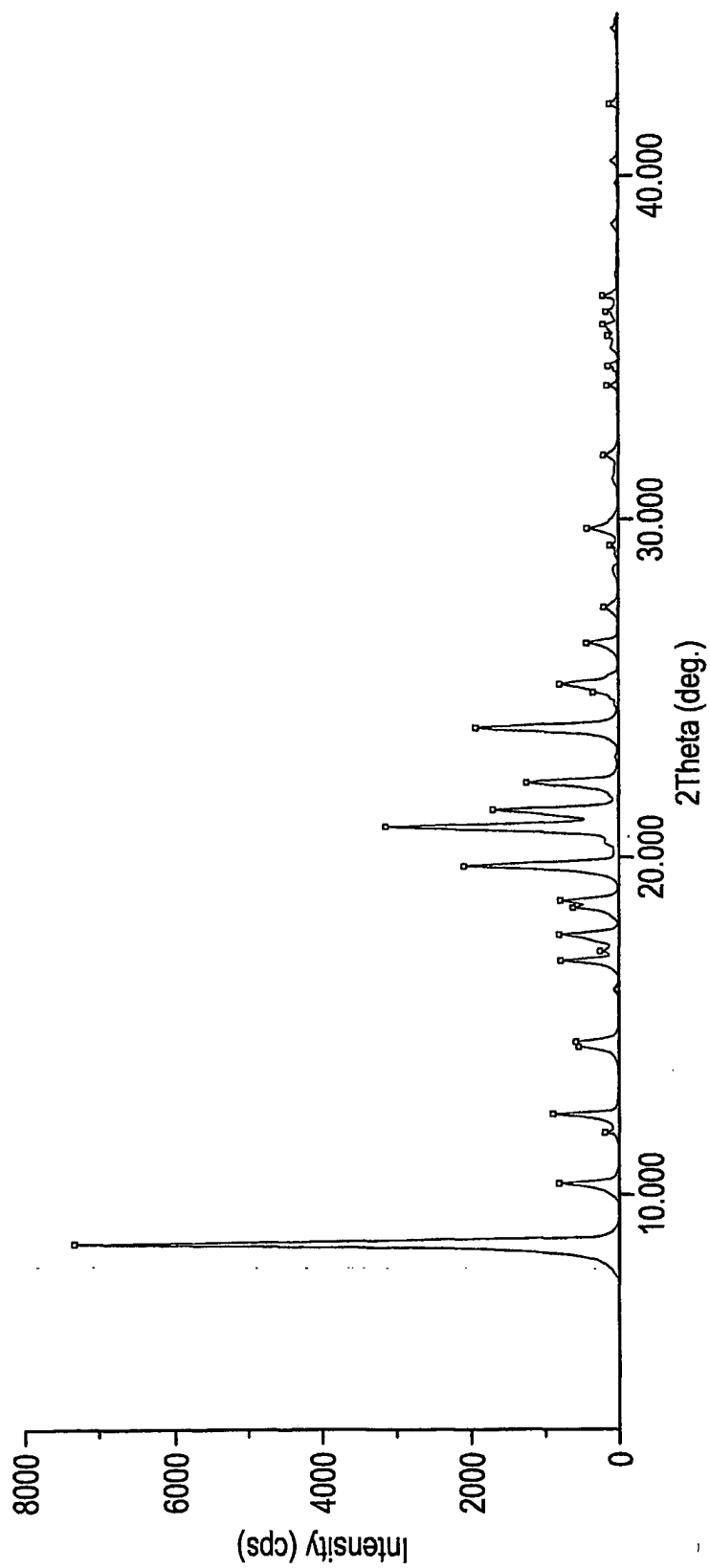
17. The process according to claim 16, wherein the amount of  
25 dichloromethane used is 4.5 to 13 volume/weight of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine hydrochloride.

- 19 -

18. The process according to claim 16, wherein in step f) the solid is washed with dichloromethane.
19. A process for preparing Olanzapine Form-I from Olanzapine Form-2 which comprises the steps of:
- 5 a) stirring 2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine hydrochloride (olanzapine Form-2) in dichloromethane at reflux to obtain a clear solution;
- b) filtering and cooling the filtrate to 0 to 5°C;
- c) stirring for 60-90 minutes; and
- d) filtering to obtain a solid, washing and drying at 60-70°C to a constant
- 10 weight.
20. The process according to claim 19, wherein the amount of dichloromethane used is 4.5 to 13 volume/weight of 2-methyl-10H-thieno-[2,3-b][1,5]benzodiazepine hydrochloride.
21. The process according to claim 19, wherein in step d) the solid is washed
- 15 with dichloromethane.

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FIG. 1A



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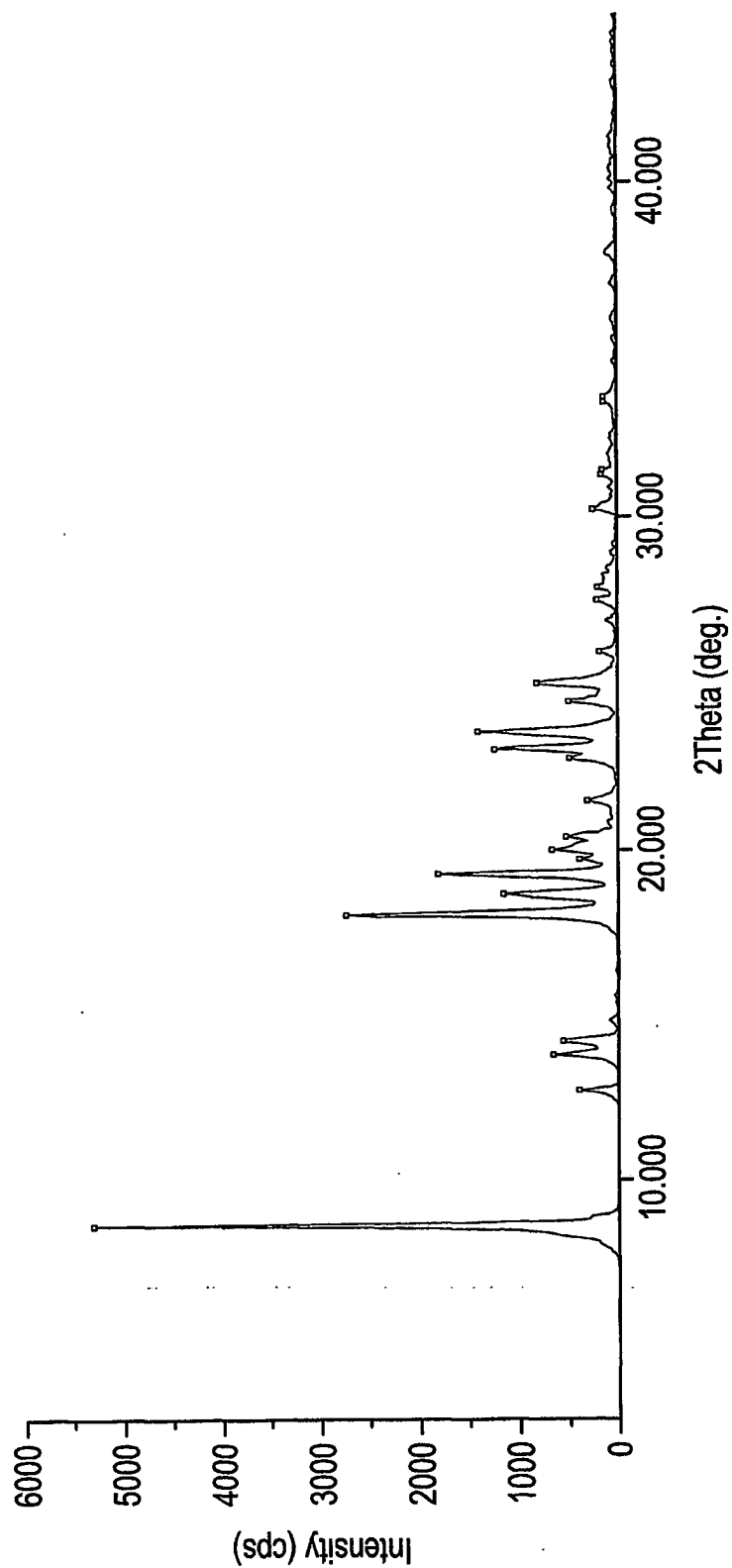
## FIG. 1B

Peak No.	2Theta	FWHM	d-value	Intensity	I/Io
1	8.620	0.165	10.2495	7305	100
2	10.360	0.141	8.5317	809	11
3	11.880	0.165	7.4433	204	3
4	12.460	0.141	7.0981	902	12
5	14.500	0.141	6.1037	543	7
6	14.640	0.141	6.0456	592	8
7	17.040	0.141	5.1992	788	11
8	17.320	0.141	5.1157	250	3
9	17.820	0.165	4.9733	812	11
10	18.620	0.141	4.7614	626	9
11	18.820	0.165	4.7113	791	11
12	19.840	0.188	4.4713	2070	28
13	20.520	0.141	4.3246	196	3
14	21.020	0.165	4.2229	3113	43
15	21.520	0.165	4.1259	1682	23
16	22.300	0.165	3.9833	1250	17
17	23.940	0.212	3.7140	1915	26
18	25.040	0.118	3.5533	361	5
19	25.240	0.188	3.5256	801	11
20	26.400	0.165	3.3732	431	6
21	27.460	0.118	3.2454	191	3
22	29.200	0.188	3.0558	129	2
23	29.720	0.165	3.0035	449	6
24	31.860	0.165	2.8065	207	3
25	33.940	0.165	2.6391	152	2
26	34.560	0.188	2.5932	114	2
27	35.420	0.118	2.5322	150	2
28	35.760	0.165	2.5089	213	3
29	36.200	0.165	2.4794	139	2
30	36.640	0.188	2.4506	185	3
31	42.260	0.188	2.1368	144	2

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FIG. 2A





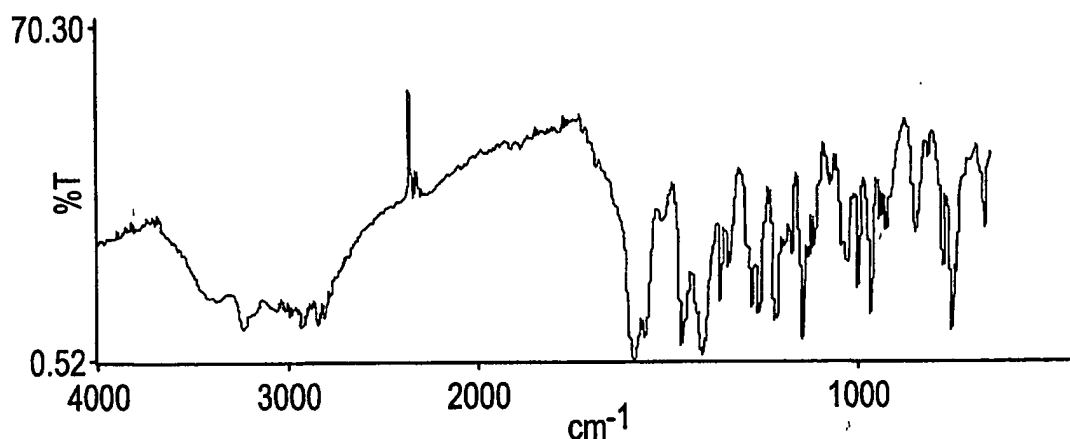
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## FIG. 2B

Peak No.	2Theta	FWHM	d-value	Intensity	I/Io
1	8.820	0.118	10.0176	5301	100
2	12.820	0.141	6.8995	385	7
3	13.920	0.188	6.3567	654	12
4	14.340	0.212	6.1714	558	11
5	18.180	0.165	4.8756	2721	51
6	18.760	0.235	4.7262	1141	22
7	19.320	0.165	4.5904	1799	34
8	19.740	0.118	4.4937	388	7
9	20.020	0.165	4.4315	663	13
10	20.440	0.188	4.3414	520	10
11	21.440	0.188	4.1411	300	6
12	22.680	0.141	3.9174	478	9
13	22.980	0.188	3.8669	1208	23
14	23.480	0.212	3.7857	1359	26
15	24.380	0.141	3.6480	489	9
16	24.920	0.212	3.5701	799	15
17	25.840	0.212	3.4451	180	3
18	27.420	0.188	3.2500	205	4
19	27.800	0.165	3.2065	200	4
20	30.120	0.141	2.9646	258	5
21	31.120	0.141	2.8715	162	3
22	31.280	0.118	2.8572	147	3
23	33.320	0.141	2.6868	134	3
24	33.480	0.118	2.6743	135	3

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FIG. 3



PEAK X 4000.0 650.0

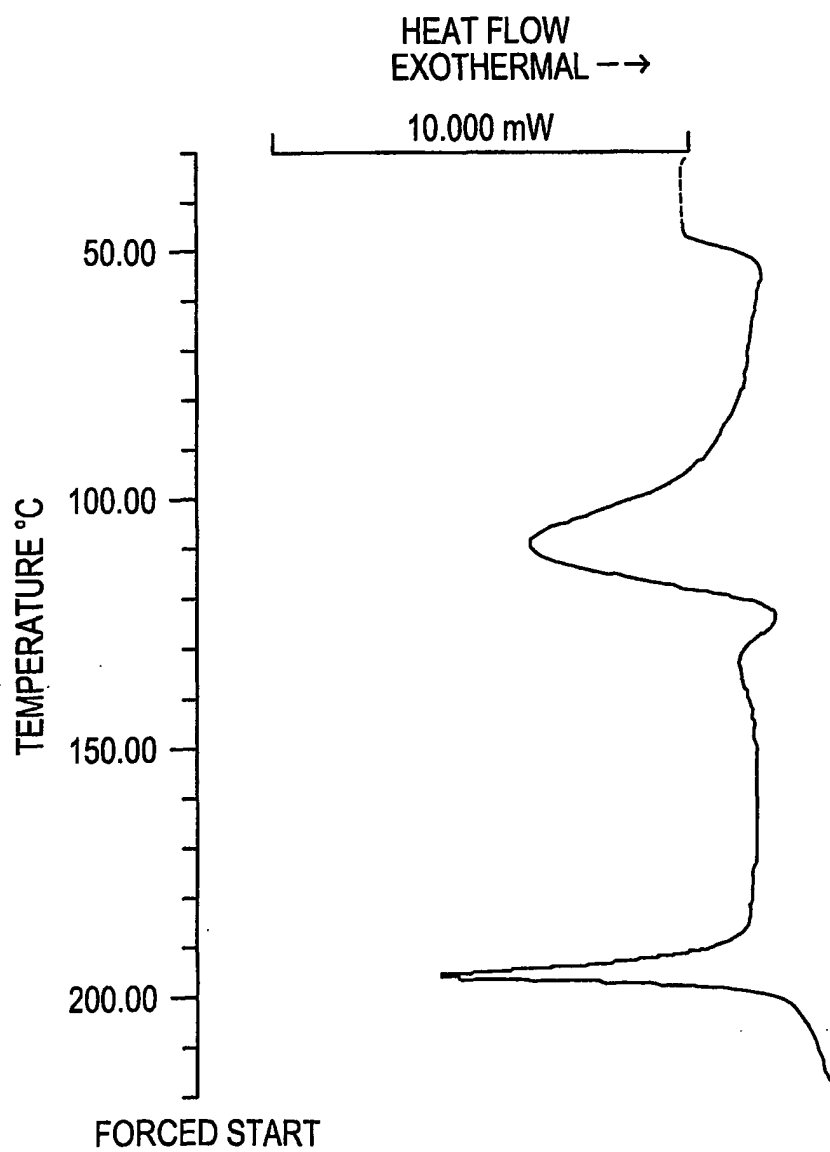
threshold 2.00%; band

cm <sup>-1</sup>	%	cm <sup>-1</sup>	%	cm <sup>-1</sup>	%	cm <sup>-1</sup>	%
3850.9	26.95	3814.5	27.40	3795.1	27.79	3742.9	28.86
3721.0	28.96	3704.6	29.14	3673.7	28.61	3654.9	27.09
3640.1	26.58	3239.0	6.83	3055.9	10.92	2933.4	7.74
2848.0	7.82	2809.6	9.05	2371.2	35.20	2357.9	32.28
2354.3	36.56	2344.0	33.79	2339.3	32.35	2331.0	34.63
2299.8	34.96	1721.7	47.98	1687.1	40.56	1657.7	37.04
1649.4	34.36	1590.2	0.52	1563.6	5.40	1556.8	8.27
1519.2	28.05	1467.4	3.78	1411.9	1.59	1367.2	12.50
1342.5	18.72	1297.4	20.57	1282.1	10.43	1265.6	10.11
1219.3	6.58	1202.0	21.99	1192.7	23.98	1179.8	19.80
1149.1	4.52	1135.2	20.40	1120.3	23.02	1084.8	38.76
1075.1	33.96	1034.4	20.40	1004.5	13.55	970.9	9.07
943.6	29.83	929.4	27.45	851.9	26.87	817.3	42.84
780.0	16.76	754.3	6.29	670.0	27.94	666.9	27.86

56 peaks found

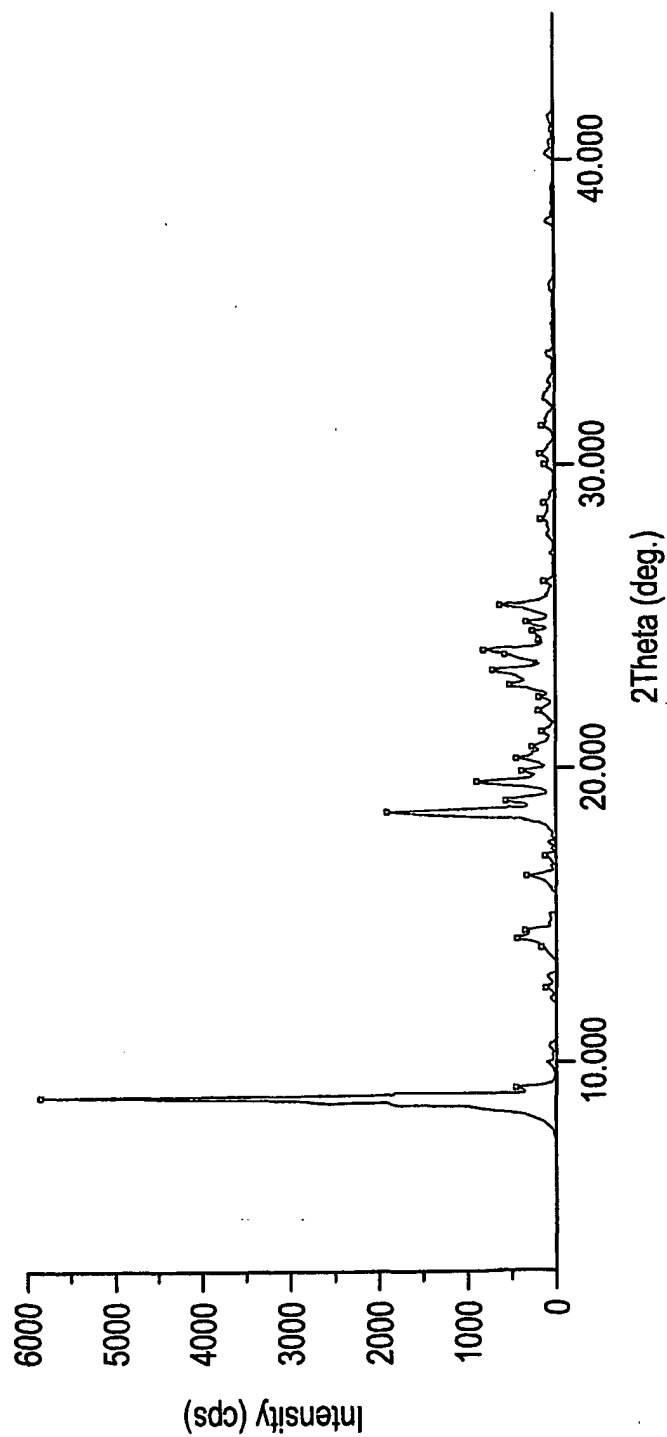
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FIG. 4



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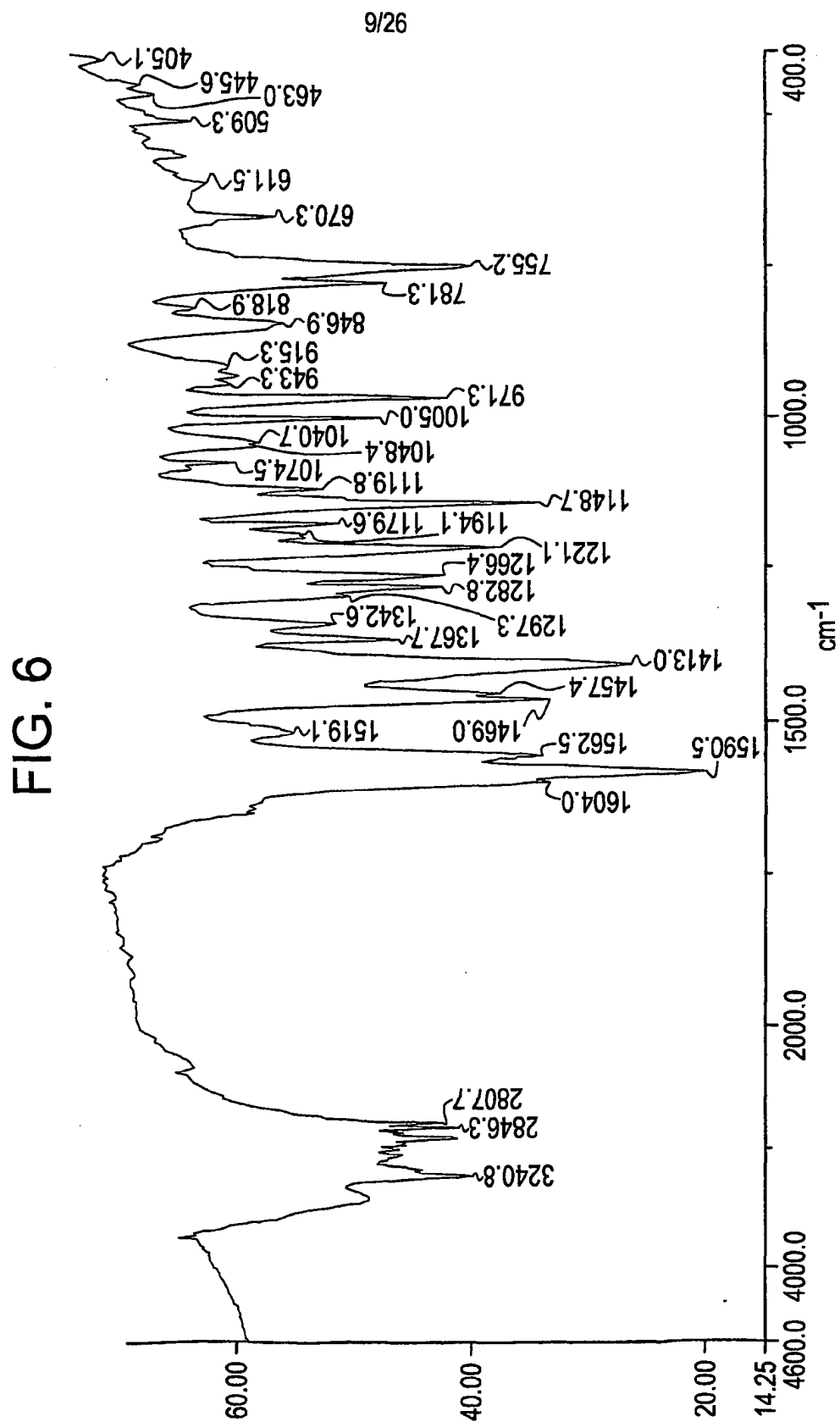
FIG. 5A



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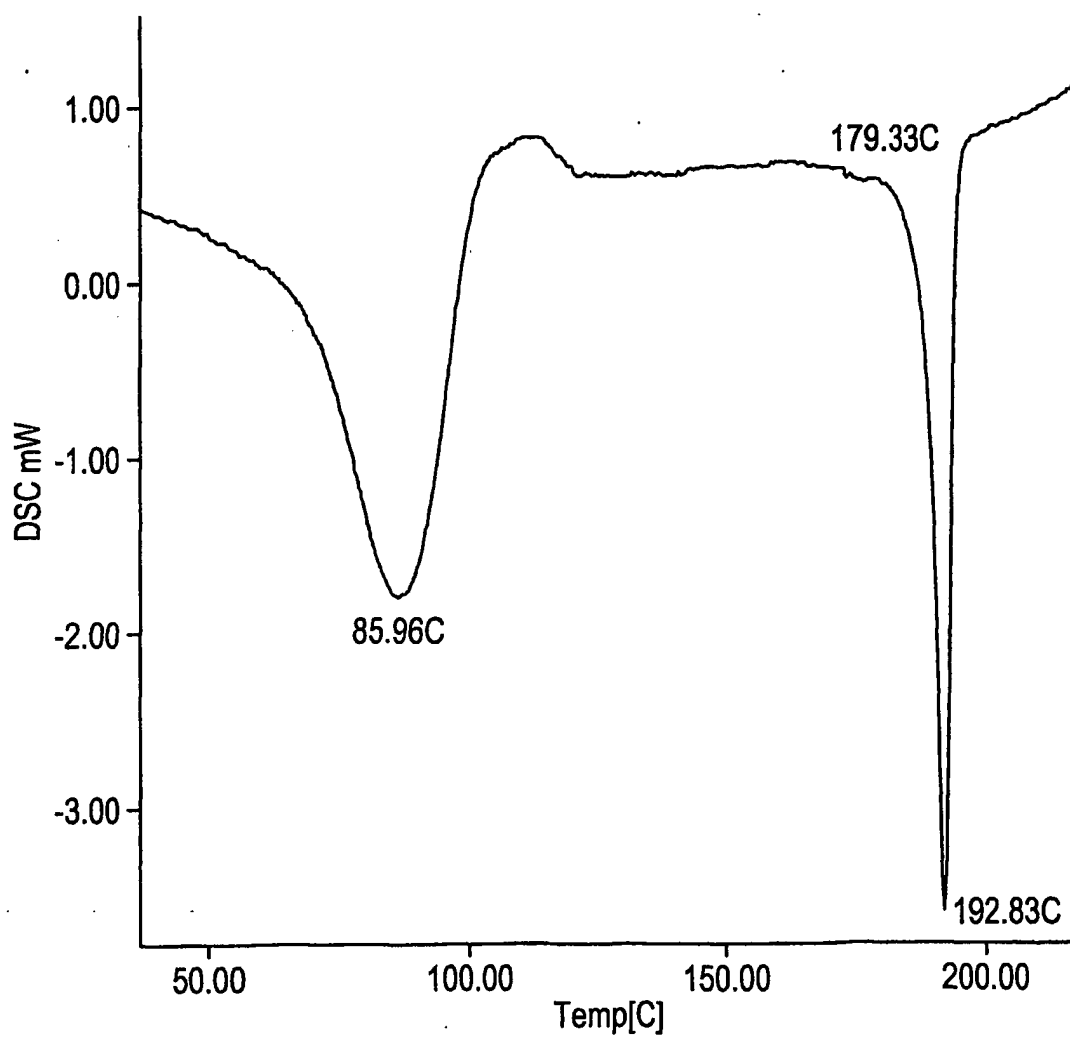
## FIG. 5B

Peak No.	2Theta	FWHM	d-value	Intensity	I/I <sub>0</sub>
1	8.840	0.165	9.9949	5867	100
2	9.120	0.141	9.6887	431	7
3	12.560	0.141	7.0418	109	2
4	13.800	0.212	6.4117	134	2
5	14.160	0.165	6.2495	426	7
6	14.460	0.118	6.1205	327	6
7	16.240	0.165	5.4534	323	6
8	16.920	0.188	5.2358	100	2
9	18.380	0.212	4.8230	1935	33
10	18.800	0.259	4.7162	551	9
11	19.400	0.188	4.5717	880	15
12	19.780	0.165	4.4847	360	6
13	20.200	0.165	4.3924	465	8
14	20.600	0.141	4.3080	241	4
15	21.100	0.212	4.2070	147	3
16	21.800	0.188	4.0735	174	3
17	22.220	0.141	3.9974	180	3
18	22.640	0.188	3.9242	505	9
19	23.120	0.212	3.8438	689	12
20	23.580	0.118	3.7699	550	9
21	23.780	0.188	3.7386	787	13
22	24.140	0.118	3.6837	177	3
23	24.360	0.165	3.6509	232	4
24	24.660	0.188	3.6072	315	5
25	25.240	0.188	3.5256	648	11
26	26.000	0.282	3.4242	101	2
27	28.060	0.212	3.1773	126	2
28	28.580	0.188	3.1207	100	2
29	29.840	0.141	2.9917	105	2
30	30.200	0.141	2.9569	158	3
31	31.100	0.212	2.8733	120	2
32	31.380	0.165	2.8483	106	2
33	32.060	0.141	2.7895	141	2



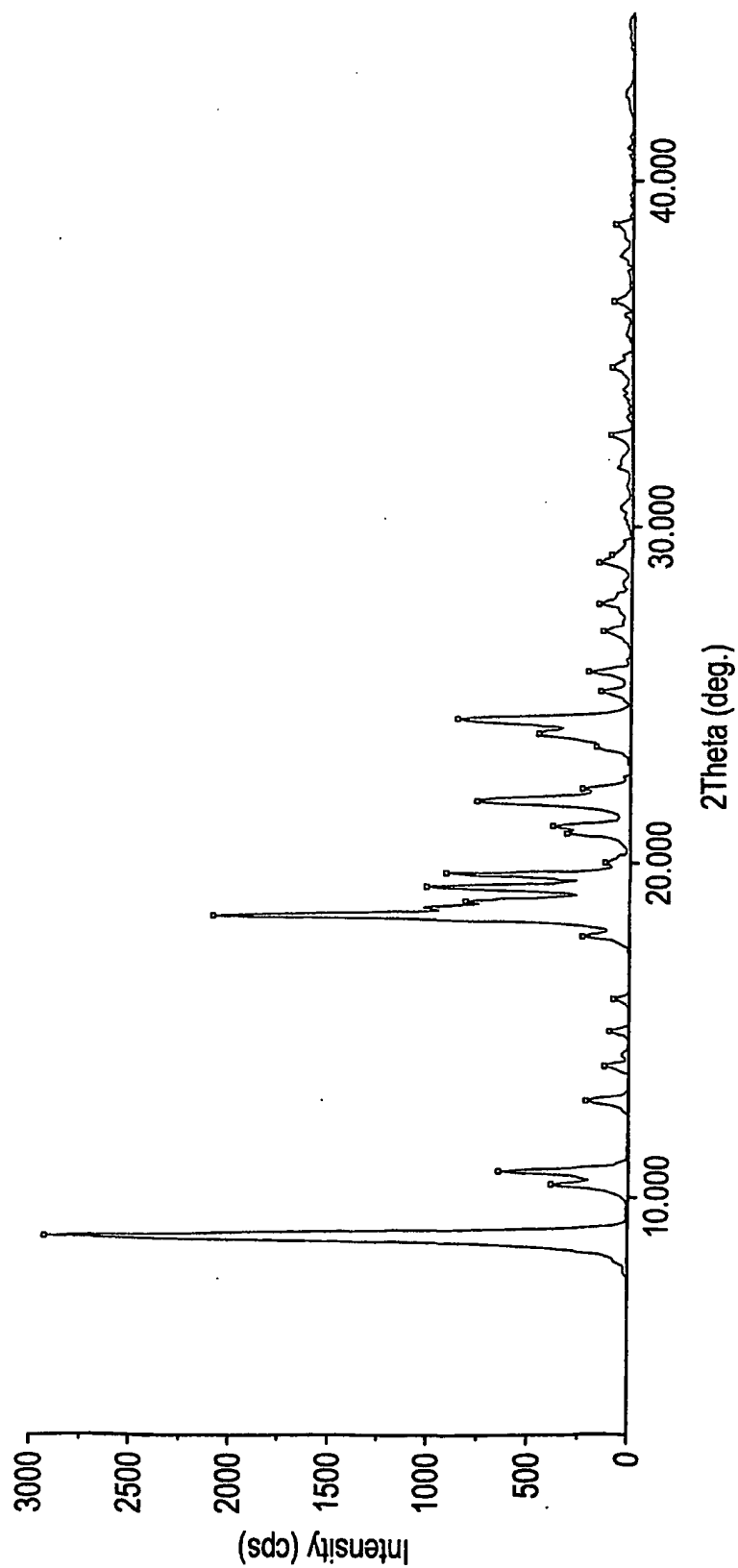
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FIG. 7



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FIG. 8A





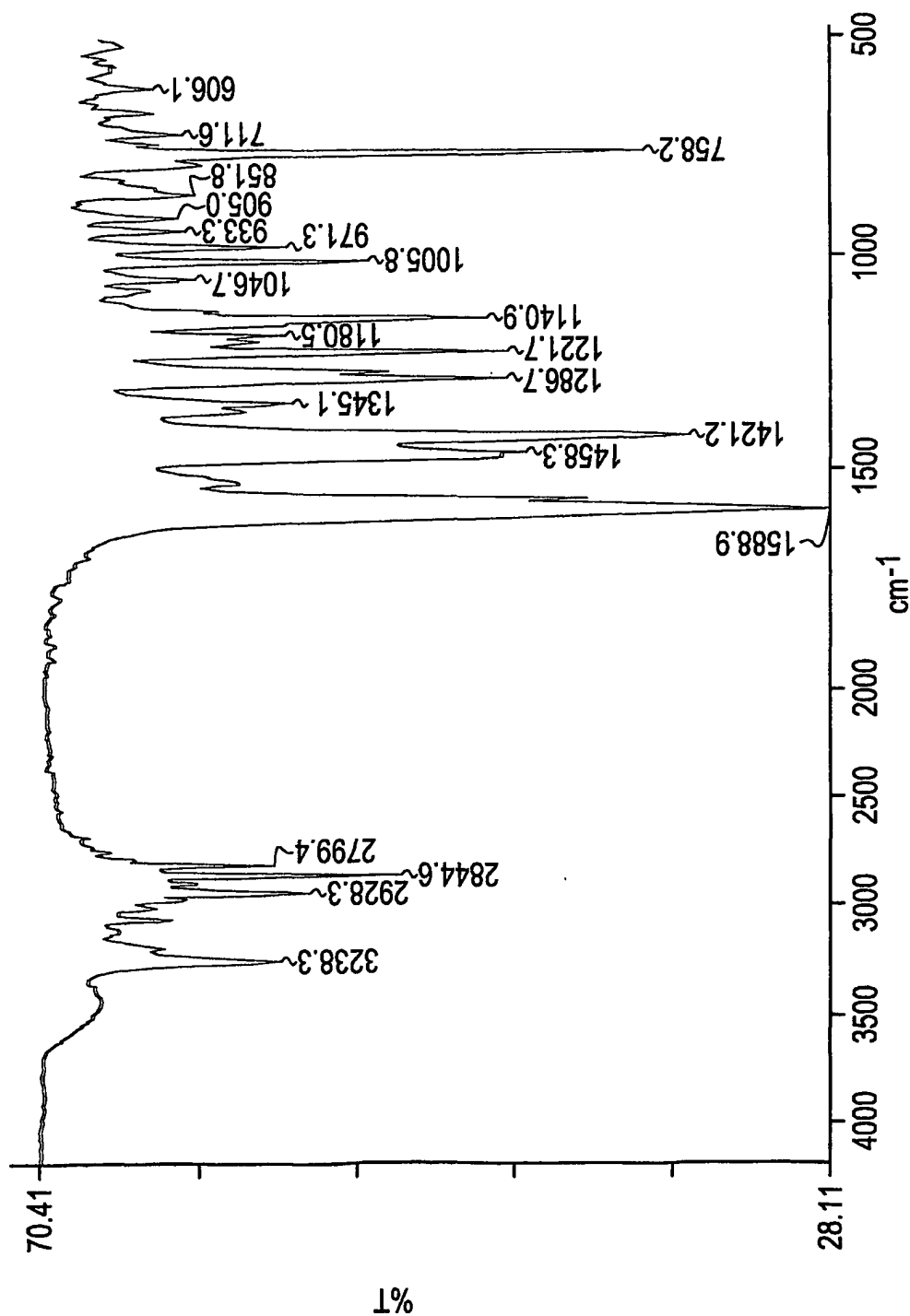
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## FIG. 8B

Peak No.	2Theta	FWHM	d-value	Intensity	I/I <sub>0</sub>
1	8.860	0.282	9.9724	2922	100
2	10.380	0.165	8.5153	392	13
3	10.780	0.188	8.2002	646	22
4	12.880	0.212	6.8675	223	8
5	13.920	0.141	6.3567	130	4
6	14.960	0.165	5.9170	104	4
7	17.820	0.165	4.9733	245	8
8	18.380	0.165	4.8230	2086	71
9	18.820	0.141	4.7113	820	28
10	19.220	0.188	4.6141	1017	35
11	19.600	0.165	4.5255	928	32
12	19.920	0.212	4.4535	122	4
13	20.800	0.141	4.2670	322	11
14	21.020	0.165	4.2229	395	14
15	21.720	0.282	4.0883	763	26
16	22.080	0.141	4.0225	249	9
17	23.260	0.212	3.8210	182	6
18	23.640	0.259	3.7604	458	16
19	24.080	0.282	3.6927	867	30
20	24.880	0.188	3.5759	166	6
21	25.460	0.212	3.4956	220	8
22	26.680	0.212	3.3385	143	5
23	27.500	0.188	3.2408	167	6
24	28.720	0.188	3.1058	166	6
25	29.020	0.118	3.0744	99	3
26	32.540	0.212	2.7494	114	4
27	34.560	0.282	2.5932	104	4
28	36.480	0.259	2.4610	98	3
29	38.680	0.212	2.3259	89	3

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FIG. 9



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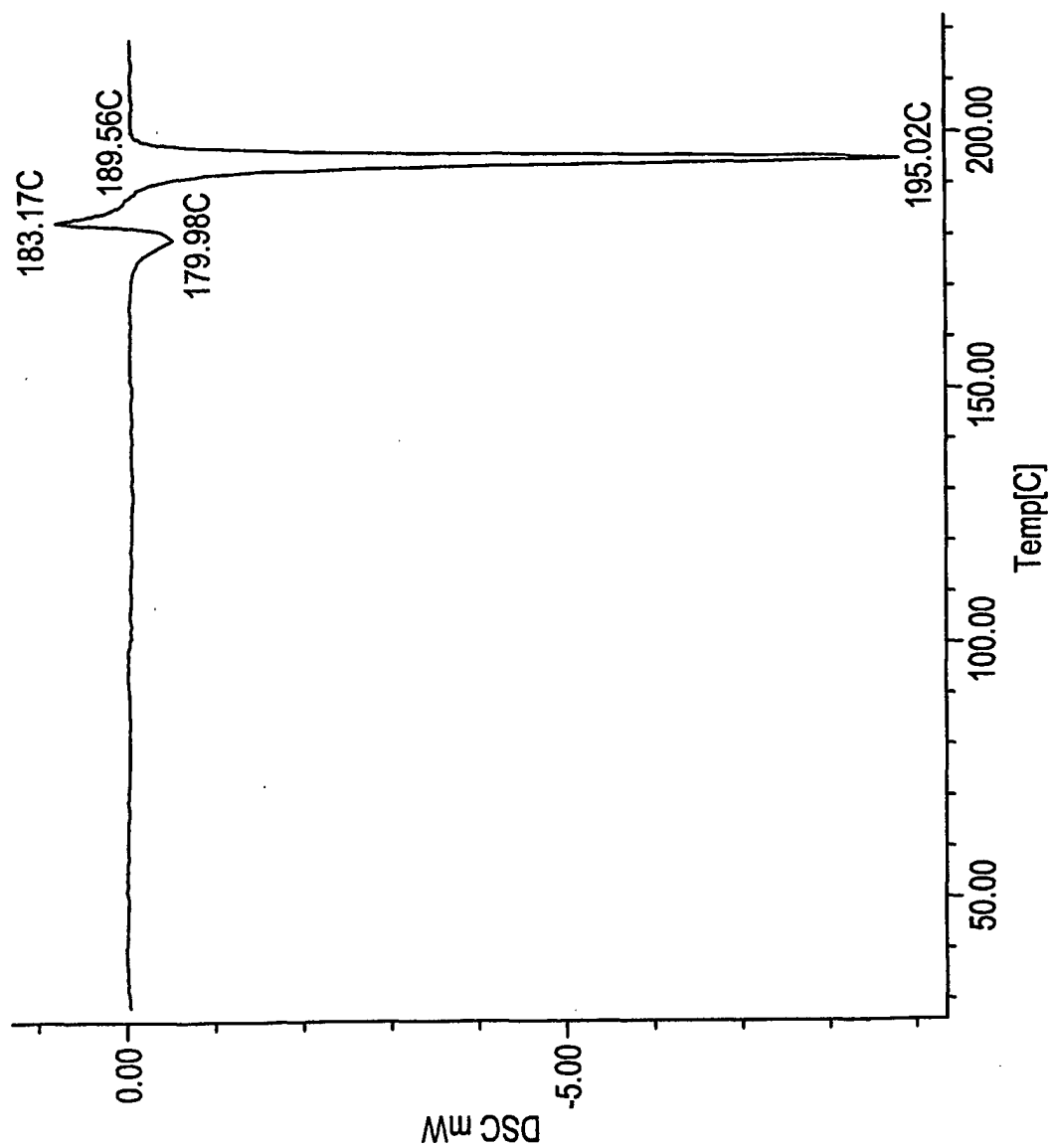
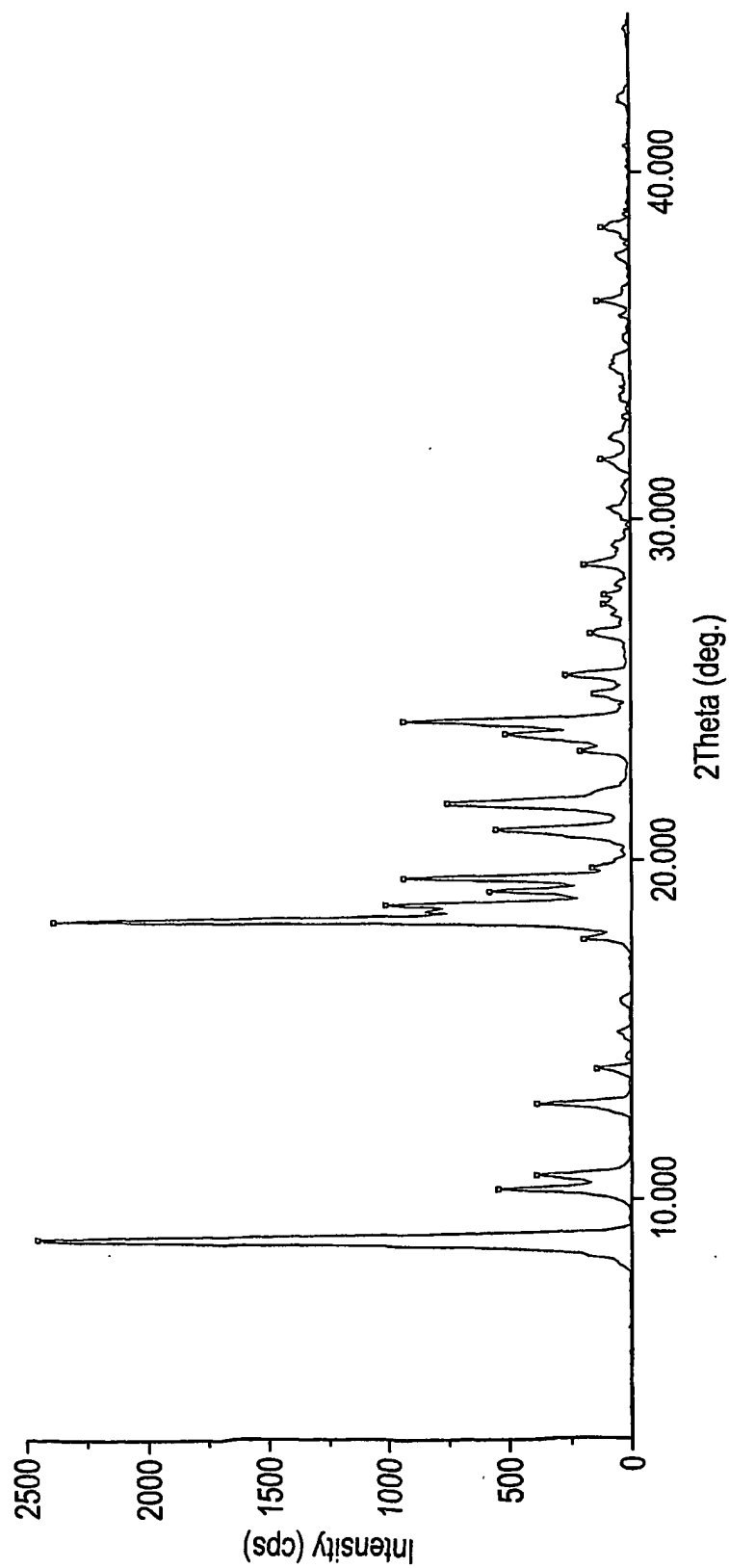


FIG. 10

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FIG. 11A



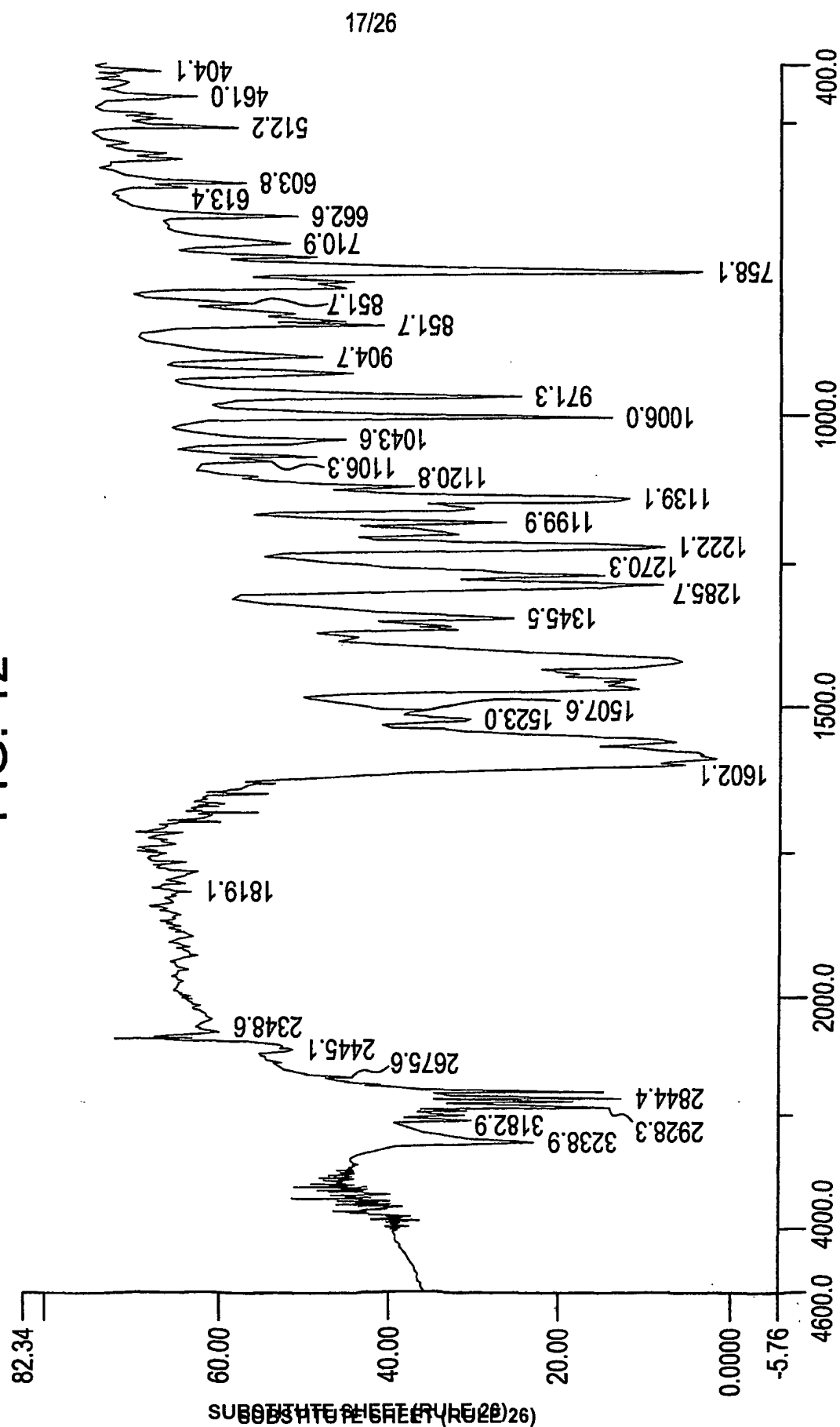
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## FIG. 11B

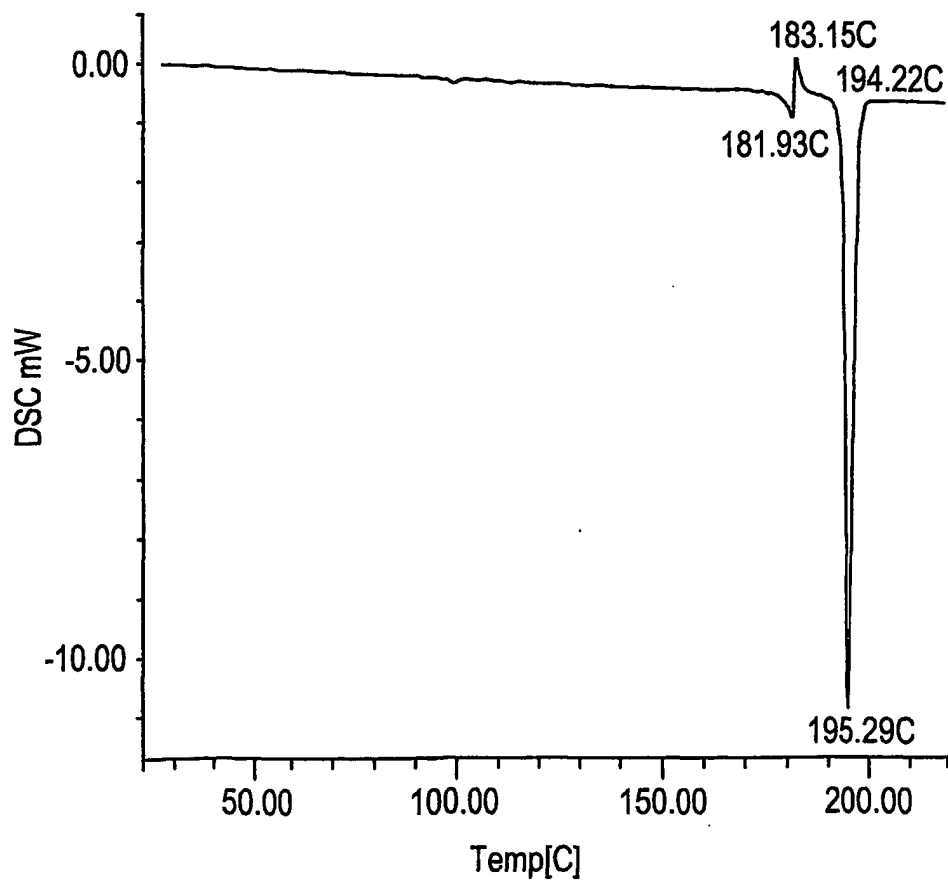
Peak No.	2Theta	FWHM	d-value	Intensity	I/Io
1	8.920	0.282	9.9055	2455	100
2	10.360	0.165	8.5317	547	22
3	10.780	0.165	8.2002	393	16
4	12.880	0.165	6.8675	396	16
5	13.940	0.141	6.3476	142	6
6	17.820	0.165	4.9733	200	8
7	18.380	0.188	4.8230	2383	97
8	18.820	0.165	4.7113	1013	41
9	19.220	0.165	4.6141	586	24
10	19.500	0.165	4.5255	939	38
11	19.900	0.188	4.4579	160	7
12	21.000	0.188	4.2268	555	23
13	21.740	0.259	4.0846	756	31
14	22.040	0.141	4.0297	159	6
15	23.260	0.188	3.8210	207	8
16	23.740	0.165	3.7448	515	21
17	24.100	0.141	3.6897	935	38
18	24.880	0.212	3.5758	154	6
19	25.460	0.235	3.4956	274	11
20	26.660	0.282	3.3409	172	7
21	27.500	0.118	3.2408	113	5
22	27.780	0.165	3.2087	104	4
23	28.700	0.259	3.1079	194	8
24	31.800	0.141	2.8117	115	5
25	36.520	0.165	2.4584	135	5
26	38.640	0.329	2.3282	117	5

FIG. 12



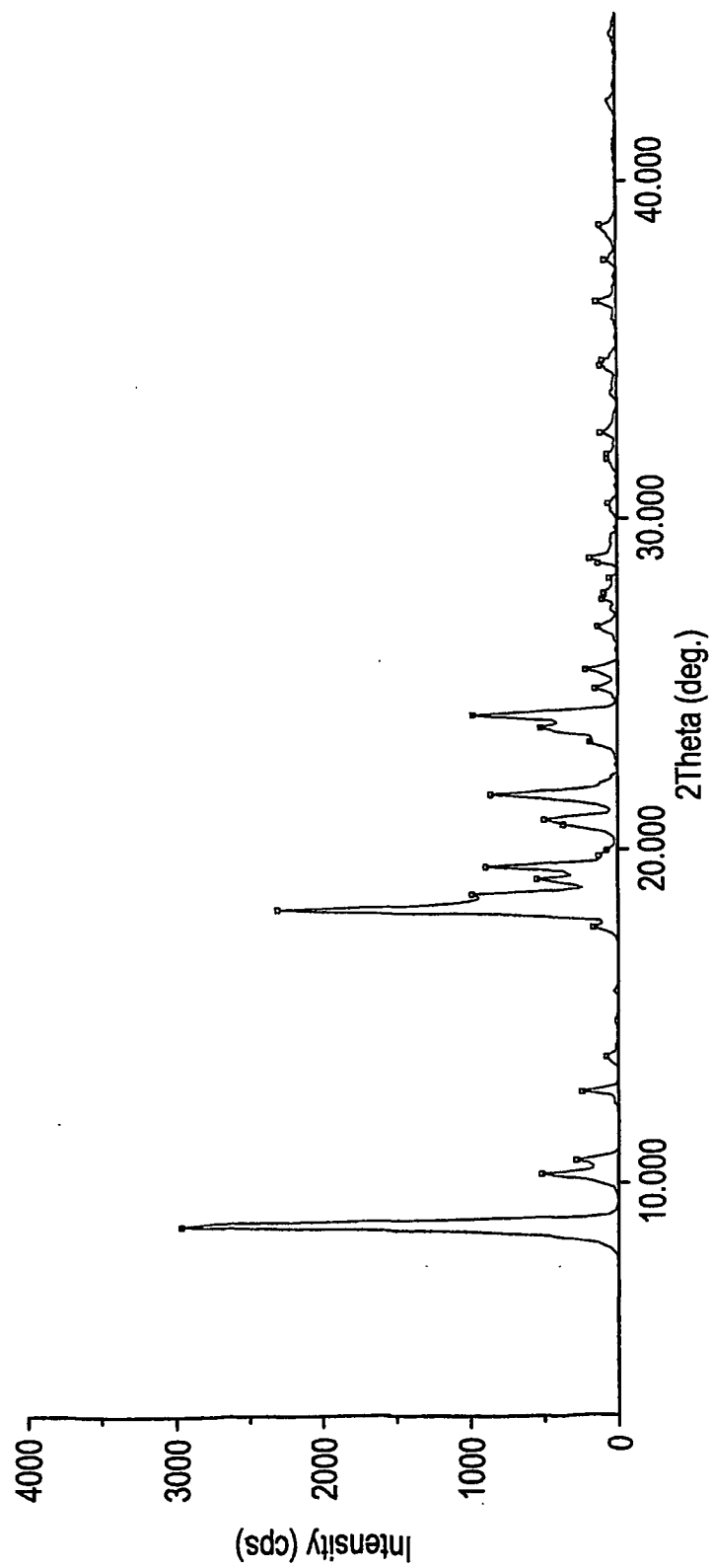
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FIG. 13



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FIG. 14A





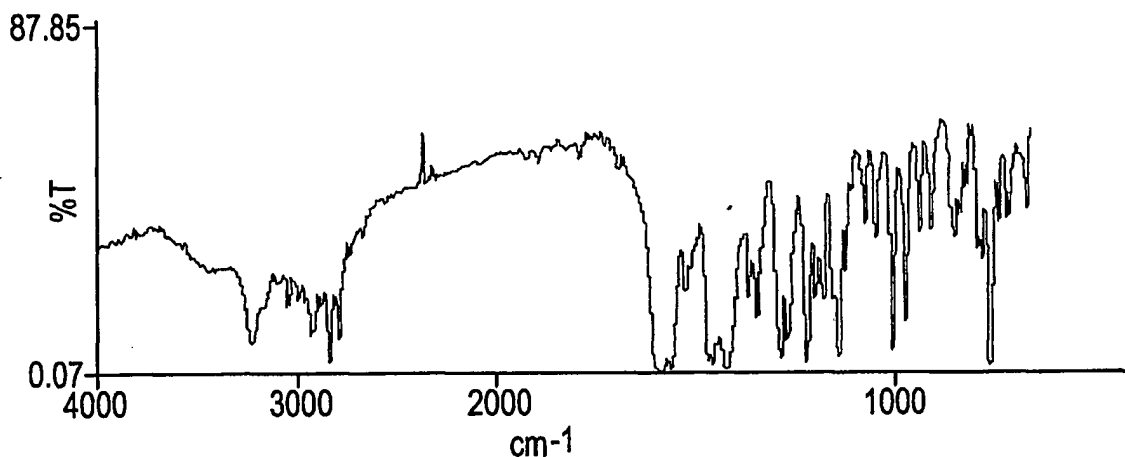
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**FIG. 14B**

Peak No.	2Theta	FWHM	d-value	Intensity	I/I <sub>0</sub>
1	8.760	0.259	10.0860	2983	100
2	10.220	0.235	8.6482	529	18
3	10.640	0.235	8.3078	312	10
4	12.740	0.259	6.9427	278	9
5	13.780	0.212	6.4210	114	4
6	17.680	0.212	5.0124	199	7
7	18.240	0.188	4.8597	2319	78
8	18.660	0.188	4.7513	999	33
9	19.100	0.212	4.6428	564	19
10	19.460	0.188	4.5577	917	31
11	19.780	0.118	4.4847	151	5
12	19.960	0.118	4.4447	79	3
13	20.700	0.118	4.2874	388	13
14	20.860	0.282	4.2549	516	17
15	21.600	0.235	4.1108	883	30
16	23.140	0.212	3.8406	206	7
17	23.560	0.282	3.7730	549	18
18	23.960	0.235	3.7109	1006	34
19	24.720	0.188	3.5985	179	6
20	25.280	0.212	3.5201	246	8
21	26.540	0.306	3.3558	160	5
22	27.340	0.188	3.2594	127	4
23	27.560	0.165	3.2338	108	4
24	27.960	0.118	3.1885	73	2
25	28.460	0.141	3.1336	145	5
26	28.600	0.141	3.1186	190	6
27	30.180	0.118	2.9588	76	3
28	31.460	0.118	2.8413	85	3
29	31.640	0.212	2.8255	85	3
30	32.320	0.188	2.7676	123	4
31	34.400	0.188	2.6049	113	4
32	34.580	0.118	2.5917	106	4
33	36.360	0.282	2.4688	136	5
34	37.580	0.141	2.3914	77	3
35	38.540	0.188	2.3340	118	4

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## FIG. 15



PEAK Y 4000.0 650.0

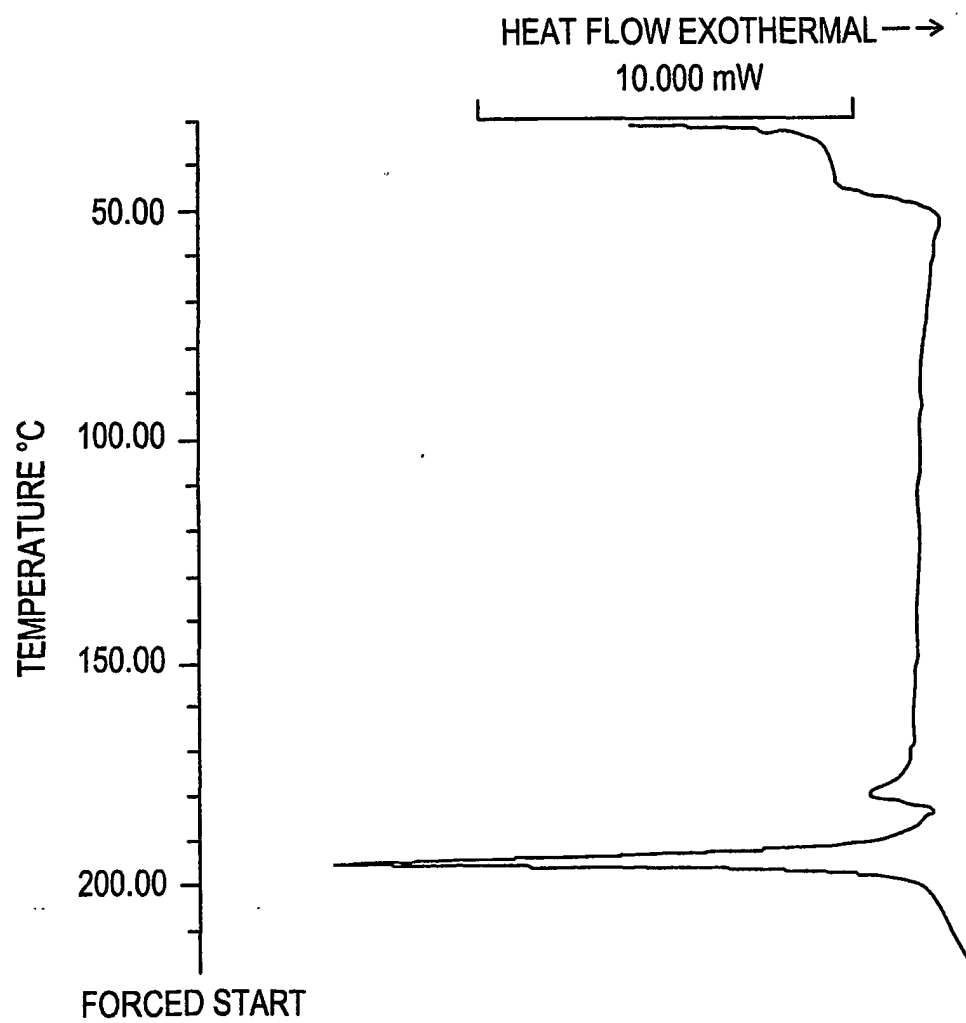
threshold 2.00%; band

cm <sup>-1</sup>	%	cm <sup>-1</sup>	%	cm <sup>-1</sup>	%	cm <sup>-1</sup>	%
3860.8	33.06	3848.0	33.03	3814.7	33.75	3795.5	34.23
3743.4	35.32	3721.0	35.09	3654.9	33.85	3238.0	6.65
3182.5	14.91	3108.8	21.85	3051.9	15.35	3005.8	16.99
2969.7	16.47	2928.1	7.10	2884.9	15.25	2843.4	2.19
2798.8	7.85	2774.9	23.08	2740.4	28.42	2674.8	32.16
2363.1	49.34	2358.9	39.06	2356.3	37.65	2344.2	46.97
2340.1	45.72	2333.0	47.30	2327.9	48.67	2301.7	48.38
1924.7	53.24	1893.8	52.45	1863.3	55.39	1819.5	55.31
1788.8	53.75	1765.8	58.32	1721.7	56.80	1692.0	50.20
1657.2	47.76	1587.7	0.07	1560.0	0.57	1524.1	18.26
1504.7	28.86	1469.5	2.11	1455.8	1.61	1418.8	0.57
1365.7	18.43	1358.2	20.70	1345.4	13.31	1285.1	1.62
1269.8	5.17	1221.6	2.05	1199.6	18.30	1179.7	13.10
1158.0	17.11	1139.1	3.78	1121.0	24.07	1105.9	45.15
1080.0	43.01	1071.5	35.95	1043.6	32.25	1005.8	5.06
971.7	12.03	935.2	31.52	931.0	29.39	905.0	35.34
851.8	26.78	845.0	33.16	833.4	39.43	817.8	45.14
787.7	30.71	777.9	28.17	757.2	0.59	735.0	36.00
711.7	38.60	679.1	53.82	672.1	53.59	667.9	42.43
662.6	36.77						

77 peaks found

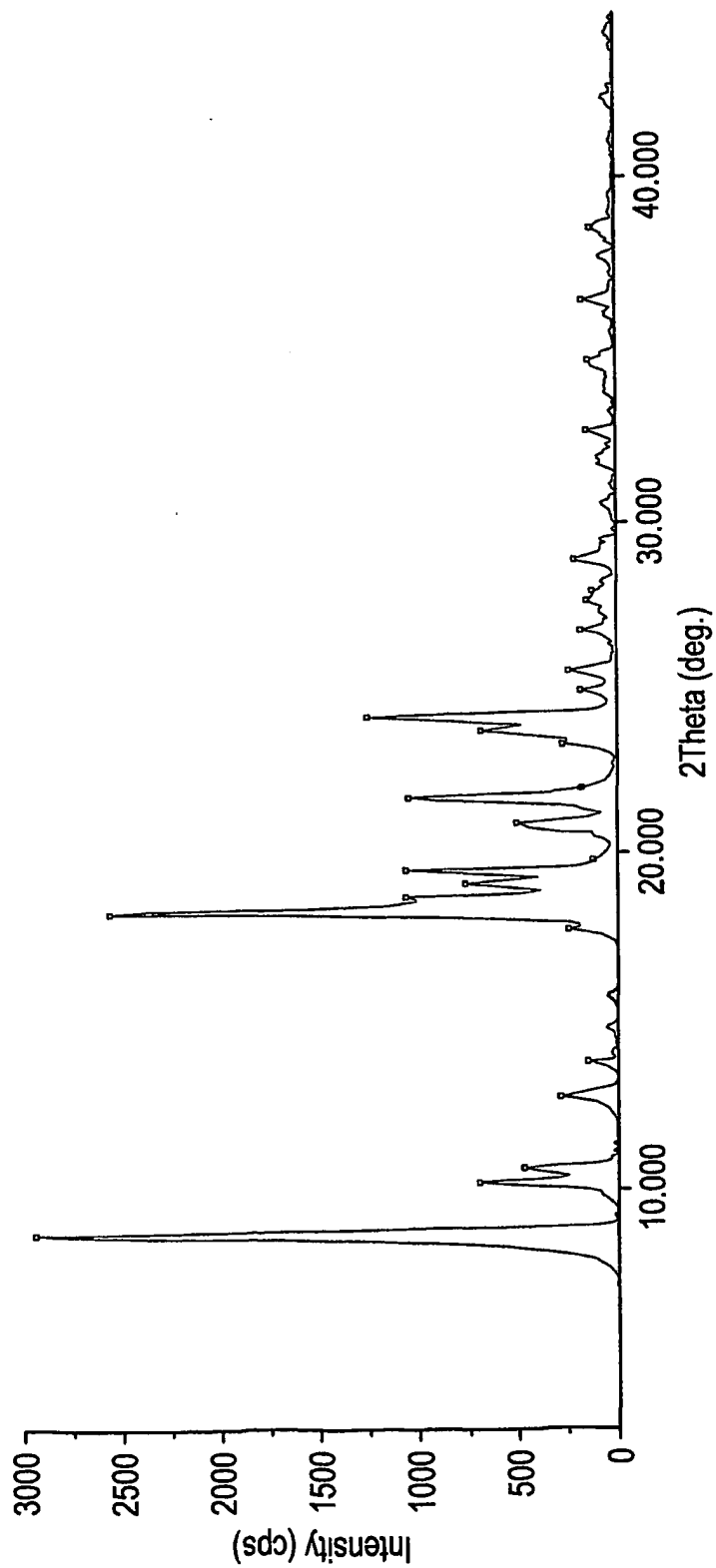
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FIG. 16



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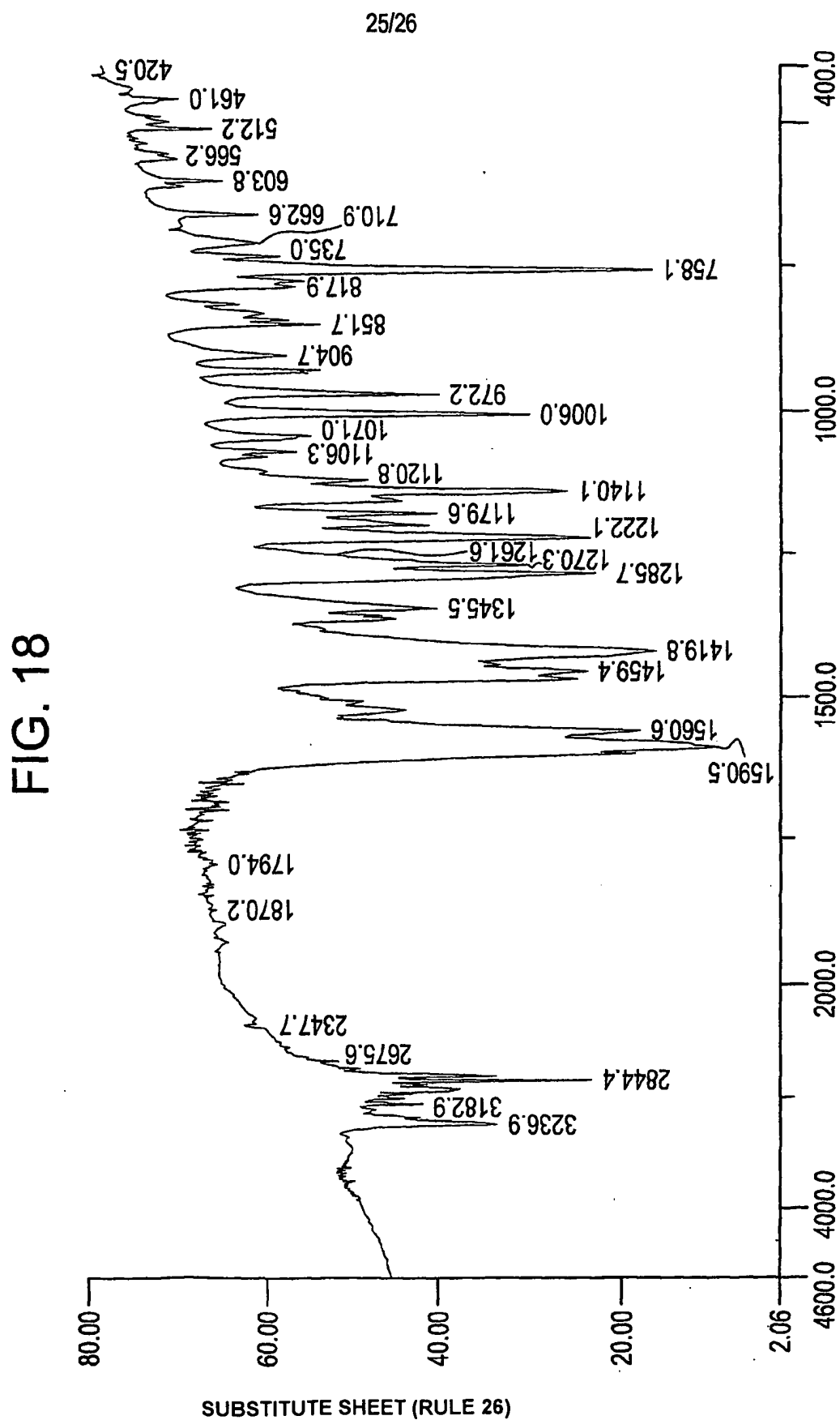
FIG. 17A



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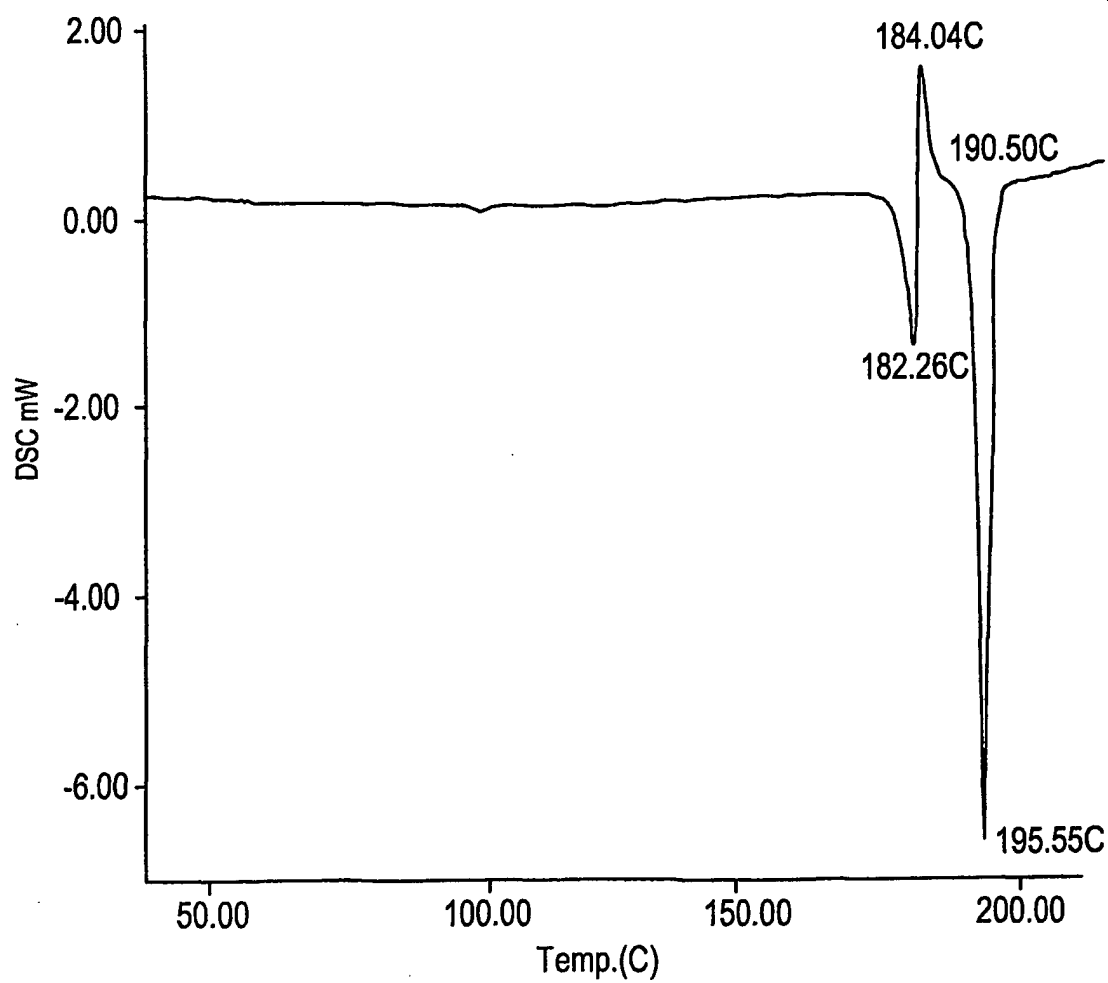
## FIG. 17B

Peak No.	2Theta	FWHM	d-value	Intensity	I/I <sub>0</sub>
1	8.860	0.282	9.9724	2932	100
2	10.340	0.212	8.5481	696	24
3	10.760	0.235	8.2154	471	16
4	12.840	0.188	6.8888	288	10
5	13.880	0.188	6.3749	152	5
6	17.780	0.188	4.9844	239	8
7	18.340	0.188	4.8335	2560	87
8	18.780	0.141	4.7212	1058	36
9	19.180	0.212	4.6236	766	26
10	19.560	0.188	4.5347	1059	36
11	19.940	0.118	4.4491	112	4
12	20.960	0.424	4.2348	502	17
13	21.680	0.212	4.0958	1045	36
14	22.040	0.118	4.0297	157	5
15	23.240	0.212	3.8243	251	9
16	23.660	0.188	3.7573	686	23
17	24.080	0.235	3.6927	1252	43
18	24.840	0.235	3.5814	184	6
19	25.400	0.212	3.5037	246	8
20	26.600	0.212	3.3483	181	6
21	27.480	0.235	3.2431	150	5
22	27.700	0.118	3.2178	121	4
23	28.660	0.212	3.1122	219	7
24	32.500	0.235	2.7527	144	5
25	34.640	0.376	2.5874	124	4
26	36.460	0.165	2.4623	165	6
27	38.580	0.165	2.3317	117	4



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FIG. 19



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/07258

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D495/04 //(C07D495/04, 333:00, 243:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 11893 A (NICHOLS JOHN R ;LARSEN SAMUEL D (US); LILLY CO ELI (US); REUTZEL S) 26 March 1998 (1998-03-26)	2
A	the whole document	1-21
X	EP 0 831 098 A (LILLY CO ELI) 25 March 1998 (1998-03-25)	2
A	cited in the application	1-21
A	the whole document	1-21
A	EP 0 733 635 A (LILLY INDUSTRIES LTD ;LILLY CO ELI (US)) 25 September 1996 (1996-09-25)	1-21
	cited in the application	
	the whole document	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

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\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

13 September 2001

Date of mailing of the international search report

20/09/2001

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/US 01/07258

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811893 A	26-03-1998	AU 720366 B	01-06-2000
		AU 4424197 A	14-04-1998
		BR 9711541 A	24-08-1999
		CN 1234738 A	10-11-1999
		CZ 9900989 A	11-08-1999
		EP 0831097 A	25-03-1998
		HU 0000065 A	28-06-2000
		JP 2001500878 T	23-01-2001
		NO 991339 A	19-03-1999
		PL 332541 A	13-09-1999
		TR 9900639 T	21-06-1999
		US 6251895 B	26-06-2001
		ZA 9708512 A	23-03-1999
EP 0831098 A	25-03-1998	AU 719441 B	11-05-2000
		AU 4484197 A	14-04-1998
		BR 9712100 A	31-08-1999
		CN 1234802 A	10-11-1999
		CZ 9900990 A	17-11-1999
		HU 0000066 A	28-06-2000
		JP 2001500877 T	23-01-2001
		NO 991382 A	22-03-1999
		PL 332482 A	13-09-1999
		TR 9900640 T	21-06-1999
		WO 9812199 A	26-03-1998
		US 6020487 A	01-02-2000
		ZA 9708515 A	23-03-1999
EP 0733635 A	25-09-1996	AP 828 A	28-04-2000
		AT 406771 B	25-08-2000
		AT 902196 A	15-01-2000
		AT 197711 T	15-12-2000
		AU 5257896 A	16-10-1996
		AU 706471 B	17-06-1999
		AU 5427996 A	16-10-1996
		BG 62619 B	31-03-2000
		BG 101900 A	31-03-1999
		BR 9607790 A	07-07-1998
		CA 2214005 A	03-10-1996
		CH 690579 A	31-10-2000
		CN 1179160 A,B	15-04-1998
		CZ 9703000 A	17-12-1997
		DE 19681286 T	02-04-1998
		DE 69611003 D	28-12-2000
		DE 69611003 T	10-05-2001
		DK 108997 A	12-11-1997
		DK 733634 T	11-12-2000
		EE 9700232 A	15-04-1998
		EP 1095941 A	02-05-2001
		EP 0733634 A	25-09-1996
		ES 2151991 T	16-01-2001
		FI 973750 A	22-09-1997
		GB 2313835 A,B	10-12-1997
		HU 9802824 A	28-06-1999
		IL 117613 A	16-07-2000
		JP 11502535 T	02-03-1999
		LT 97148 A,B	26-01-1998
		LU 90096 A	22-07-1997

# INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Int ional Application No  
PCT/US 01/07258

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0733635 A		LV 12018 A	20-04-1998
		LV 12018 B	20-09-1998
		NO 974365 A	22-09-1997
		NZ 306110 A	24-09-1998
		PL 322501 A	02-02-1998
		PT 733634 T	30-04-2001
		SE 9703205 A	05-09-1997
		SI 9620040 A	30-06-1998
		SI 733634 T	30-06-2001
		SK 121897 A	04-03-1998
		TR 9701017 T	21-01-1998
		WO 9630374 A	03-10-1996
		WO 9630375 A	03-10-1996
		US 5736541 A	07-04-1998